

Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein)

*Prevnar*TM

Rx only

For Intramuscular Injection Only

DESCRIPTION

*Prevnar*TM, Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein), is a sterile solution of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to diphtheria CRM₁₉₇ protein. Each serotype is grown in soy peptone broth. The individual polysaccharides are purified through centrifugation, precipitation, ultrafiltration, and column chromatography. The polysaccharides are chemically activated to make saccharides which are directly conjugated to the protein carrier CRM₁₉₇ to form the glycoconjugate. This is effected by reductive amination. CRM₁₉₇ is a nontoxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* strain C7 (β197) grown in a casamino acids and yeast extract-based medium. CRM₁₉₇ is purified through ultrafiltration, ammonium sulfate precipitation, and ion-exchange chromatography. The individual glycoconjugates are purified by ultrafiltration and column chromatography and are analyzed for saccharide to protein ratios, molecular size, free saccharide, and free protein.

The individual glycoconjugates are compounded to formulate the vaccine, *Prevnar*TM. Potency of the formulated vaccine is determined by quantification of each of the saccharide antigens, and by the saccharide to protein ratios in the individual glycoconjugates.

*Prevnar*TM is manufactured as a liquid preparation. Each 0.5 mL dose is formulated to contain: 2 µg of each saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F, and 4 µg of

serotype 6B per dose (16 µg total saccharide); approximately 20 µg of CRM₁₉₇ carrier protein; and 0.125 mg of aluminum per 0.5 mL dose as aluminum phosphate adjuvant.

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After shaking, the vaccine is a homogeneous, white suspension.

CLINICAL PHARMACOLOGY

40 *S. pneumoniae* is an important cause of morbidity and mortality in persons of all ages worldwide. The organism causes invasive infections, such as bacteremia and meningitis, as well as pneumonia and upper respiratory tract infections including otitis media and sinusitis. In children older than 1 month, *S. pneumoniae* is the most common cause of invasive disease.¹ Data from community-based studies performed between 1986 and
45 1995, indicate that the overall annual incidence of invasive pneumococcal disease in the United States is an estimated 10 to 30 cases per 100,000 persons, with the highest risk in children aged less than or equal to 2 years of age (140 to 160 cases per 100,000 persons).^{2,3,4,5,6} Children in group child care have an increased risk for invasive pneumococcal disease.^{7,8} Immunocompromised individuals with neutropenia, asplenia,
50 sickle cell disease, disorders of complement and humoral immunity, human immunodeficiency virus (HIV) infections or chronic underlying disease are also at increased risk for invasive pneumococcal disease.⁸ *S. pneumoniae* is the most common cause of bacterial meningitis in the United States.¹ The annual incidence of pneumococcal meningitis in children between 1 to 23 months of age is approximately 7
55 cases per 100,000 persons.¹ Pneumococcal meningitis in childhood has been associated with 8% mortality and may result in neurological sequelae (25%) and hearing loss (32%) in survivors.⁹

S. pneumoniae is an important cause of acute otitis media, identified in 20 to 40% of
60 middle ear fluid cultures.^{10,11} The seven serotypes account for approximately 60% of acute otitis media due to *S. pneumoniae* (12-24% of all acute otitis media).¹² The exact contribution of *S. pneumoniae* to childhood pneumonia is unknown, as it is often not possible to identify the causative organisms. In studies of children less than 5 years of age with community-acquired pneumonia, where diagnosis was attempted using

65 serological methods, antigen testing, or culture data, 30% of cases were classified as
bacterial pneumonia, and 70% of these (21% of total community-acquired pneumonia)
were found to be due to *S. pneumoniae*.^{13,14}

In the past decade the proportion of *S. pneumoniae* isolates resistant to antibiotics has
70 been on the rise in the United States and worldwide. In a multi-center US surveillance
study, the prevalence of penicillin and cephalosporin-nonsusceptible (intermediate or
high level resistance) invasive disease isolates from children was 21% (range < 5% to
38% among centers), and 9.3% (range 0-18%), respectively. Over the 3-year surveillance
period (1993-1996), there was a 50% increase in penicillin-nonsusceptible *S. pneumoniae*
75 (PNSP) strains and a three-fold rise in cephalosporin-nonsusceptible strains.⁸ Although
generally less common than PNSP, pneumococci resistant to macrolides and
trimethoprin-sulfazoxole have also been observed.⁴ Day care attendance, a history of ear
infection, and a recent history of antibiotic exposure, have also been associated with
invasive infections with PNSP in children 2 months to 59 months of age.^{7,8} There has
80 been no difference in mortality associated with PNSP strains.^{8,9} However, the American
Academy of Pediatrics (AAP) revised the antibiotic treatment guidelines in 1997 in
response to the increased prevalence of antibiotic-resistant pneumococci.¹⁵

Approximately 90 serotypes of *S. pneumoniae* have been identified based on antigenic
85 differences in their capsular polysaccharides. The distribution of serotypes responsible
for disease differ with age and geographic location.¹⁶

Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F have been responsible for approximately
80% of invasive pneumococcal disease in children < 6 years of age in the United States.¹²
90 These 7 serotypes also accounted for 74 % of PNSP and 100% of pneumococci with high
level penicillin resistance isolated from children < 6 years with invasive disease during a
1993-1994 surveillance by the Centers for Disease Control.¹⁷

Results of Clinical Evaluations

95 Efficacy

Efficacy was assessed in a randomized, double-blinded clinical trial in a multiethnic population at Northern California Kaiser Permanente (NCKP) beginning in October 1995, in which 37,816 infants were randomized to receive either Prevnar™ or a control vaccine (an investigational meningococcal group C conjugate vaccine [MnCC]) at 2, 4, 6, and 12-
100 15 months of age. Prevnar™ was administered to 18,906 children and the control vaccine to 18,910 children. Routinely recommended vaccines were also administered which changed during the trial to reflect changing AAP and Advisory Committee on Immunization Practices (ACIP) recommendations. A planned interim analysis was performed upon accrual of 17 cases of invasive disease due to vaccine-type *S. pneumoniae*
105 (August 1998). Ancillary endpoints for evaluation of efficacy against pneumococcal disease were also assessed in this trial.

Efficacy against invasive disease: Invasive disease was defined as isolation and identification of *S. pneumoniae* from normally sterile body sites in children presenting with an acute illness consistent with pneumococcal disease. Weekly surveillance of
110 listings of cultures from the NCKP Regional Microbiology database was conducted to assure ascertainment of all cases. The primary endpoint was efficacy against invasive pneumococcal disease due to vaccine serotypes. The per protocol analysis of the primary endpoint included cases which occurred ≥ 14 days after the third dose. The intent-to-treat (ITT) analysis included all cases of invasive pneumococcal disease due to vaccine
115 serotypes in children who received at least one dose of vaccine. Secondary analyses of efficacy against all invasive pneumococcal disease, regardless of serotype, were also performed according to these same per protocol and ITT definitions. Results of these analyses are presented in Table 1.

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TABLE 1
Efficacy of Prevnar™ Against Invasive Disease Due to *S. pneumoniae*
in Cases Accrued From October 15, 1995 Through August 20, 1998^{18,19}

| | Prevnar™ Number of Cases | Control* Number of Cases | Efficacy | 95% CI |
|----------------------------|-----------------------------|--------------------------------|----------|------------|
| Vaccine serotypes | | | | |
| Per protocol | 0 | 17 | 100% | 75.4, 100 |
| Intent-to-treat | 0 | 22 | 100% | 81.7, 100 |
| All pneumococcal serotypes | | | | |
| Per protocol | 2 | 20 | 90.0% | 58.3, 98.9 |
| Intent-to-treat | 3 | 27† | 88.9% | 63.8, 97.9 |

*Investigational meningococcal group C conjugate vaccine (MnCC).

†Includes one case in an immunocompromised subject.

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All 22 cases of invasive disease due to vaccine serotype strains in the ITT population were bacteraemic. In addition, the following diagnoses were also reported: meningitis (2), pneumonia (2), and cellulitis (1).

130 Preliminary efficacy data through an extended follow-up period to April 20, 1999, resulted in a similar efficacy estimate (Per protocol: 1 case in Prevnar™ group, 39 cases in control group; ITT: 3 cases in Prevnar™ group, 49 cases in the control group).

135 Immunogenicity

Routine Schedule

140 Subjects from a subset of selected study sites in the NCKP efficacy study were approached for participation in the immunogenicity portion of the study on a volunteer basis. Immune responses following three or four doses of Prevnar™ or the control vaccine were evaluated in children who received either concurrent Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Haemophilus b Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein Conjugate), (DTP-HbOC), or Diphtheria and Tetanus

Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP), and Haemophilus b

145 Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein Conjugate), (HbOC) vaccines at 2, 4, and 6 months of age. The use of Hepatitis B (Hep B), Oral Polio Vaccine (OPV), Inactivated Polio Vaccine (IPV), Measles-Mumps-Rubella (MMR), and Varicella vaccines were permitted according to the AAP and ACIP recommendations.

150 Table 2 presents the geometric mean concentrations (GMC) of pneumococcal antibodies following the third and fourth doses of Prevnar™ or the control vaccine when administered concurrently with DTP-HbOC vaccine in the efficacy study.

TABLE 2
Geometric Mean Concentrations (μg/mL) of Pneumococcal Antibodies Following the Third and Fourth Doses of Prevnar™ or Control* When Administered Concurrently With DTP-HbOC in the Efficacy Study¹⁹

| Serotype | Post dose 3 GMC [†] (95% CI for Prevnar™) | | Post dose 4 GMC [‡] (95% CI for Prevnar™) | |
|----------|---|----------|---|----------|
| | Prevnar™§ | Control* | Prevnar™§ | Control* |
| | N=88 | N=92 | N=68 | N=61 |
| 4 | 1.46 (1.19, 1.78) | 0.03 | 2.38 (1.88, 3.03) | 0.04 |
| 6B | 4.70 (3.59, 6.14) | 0.08 | 14.45 (11.17, 18.69) | 0.17 |
| 9V | 1.99 (1.64, 2.42) | 0.05 | 3.51 (2.75, 4.48) | 0.06 |
| 14 | 4.60 (3.70, 5.74) | 0.05 | 6.52 (5.18, 8.21) | 0.06 |
| 18C | 2.16 (1.73, 2.69) | 0.04 | 3.43 (2.70, 4.37) | 0.07 |
| 19F | 1.39 (1.16, 1.68) | 0.09 | 2.07 (1.66, 2.57) | 0.18 |
| 23F | 1.85 (1.46, 2.34) | 0.05 | 3.82 (2.85, 5.11) | 0.09 |

* Control was investigational meningococcal group C conjugate vaccine (MnCC).

† Mean age of Prevnar™ group was 7.8 months and of control group was 7.7 months.
N is slightly less for some serotypes in each group.

‡ Mean age of Prevnar™ group was 14.2 months and of control group was 14.4 months.
N is slightly less for some serotypes in each group.

§ p<0.001 when Prevnar™ compared to control for each serotype using a Wilcoxon's test.

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In another randomized study (Manufacturing Bridging Study, 118-16), immune responses were evaluated following three doses of Prevnar™ administered concomitantly with

DTaP and HbOC vaccines at 2, 4, and 6 months of age, IPV at 2 and 4 months of age, and Hep B at 2 and 6 months of age. The control group received concomitant vaccines only.

160 Table 3 presents the immune responses to pneumococcal polysaccharides observed in both this study and in the subset of subjects from the efficacy study that received concomitant DTaP and HbOC vaccines.

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TABLE 3
Geometric Mean Concentrations ($\mu\text{g/mL}$) of Pneumococcal Antibodies Following the Third Dose of PrevnarTM or Control^{*} When Administered Concurrently With DTaP and HbOC in the Efficacy Study[†] and Manufacturing Bridging Study^{19,20}

| Serotype | Efficacy Study | | Manufacturing Bridging Study | |
|----------|---|----------------------|---|----------------------|
| | Post dose 3 GMC [‡] (95% CI for Prevnar TM) | | Post dose 3 GMC [§] (95% CI for Prevnar TM) | |
| | Prevnar TM | Control [*] | Prevnar TM | Control [*] |
| | N=32 | N=32 | N=159 | N=83 |
| 4 | 1.47 (1.08, 2.02) | 0.02 | 2.03 (1.75, 2.37) | 0.02 |
| 6B | 2.18 (1.20, 3.96) | 0.06 | 2.97 (2.43, 3.65) | 0.07 |
| 9V | 1.52 (1.04, 2.22) | 0.04 | 1.18 (1.01, 1.39) | 0.04 |
| 14 | 5.05 (3.32, 7.70) | 0.04 | 4.64 (3.80, 5.66) | 0.04 |
| 18C | 2.24 (1.65, 3.02) | 0.04 | 1.96 (1.66, 2.30) | 0.04 |
| 19F | 1.54 (1.09, 2.17) | 0.10 | 1.91 (1.63, 2.25) | 0.08 |
| 23F | 1.48 (0.97, 2.25) | 0.05 | 1.71 (1.44, 2.05) | 0.05 |

* Control in efficacy study was investigational meningococcal group C conjugate vaccine (MnCC) and in Manufacturing Bridging Study was concomitant vaccines only.

† Sufficient data are not available to reliably assess GMCs following 4 doses of PrevnarTM when administered with DTaP in the NCKP efficacy study.

‡ Mean age of the PrevnarTM group was 7.4 months and of the control group was 7.6 months. N is slightly less for some serotypes in each group.

§ Mean age of the PrevnarTM group and the control group was 7.2 months.

|| $p < 0.001$ when PrevnarTM compared to control for each serotype using a Wilcoxon's test in the efficacy study and two-sample t-test in the Manufacturing Bridging Study.

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In all studies in which the immune responses to Prevnar™ were contrasted to control, a significant antibody response was seen to all vaccine serotypes following three or four doses, although geometric mean concentrations of antibody varied among

175 serotypes.^{18,19,20,21,22,23,24,25} The minimum serum antibody concentration necessary for protection against invasive pneumococcal disease has not been determined for any serotype. Prevnar™ induces functional antibodies to all vaccine serotypes, as measured by opsonophagocytosis following three doses.²⁵

180 Previously Unvaccinated Older Infants and Children

To determine an appropriate schedule for children 7 months of age or older at the time of the first immunization with Prevnar™, 483 children in 4 ancillary studies received Prevnar™ at various schedules. GMCs attained using the various schedules among older infants and children were comparable to immune responses of children, who received
185 concomitant DTaP, in the NCKP efficacy study (118-8) after 3 doses for most serotypes, as shown in Table 4. These data support the schedule for previously unvaccinated older infants and children who are beyond the age of the infant schedule. For usage in older infants and children see DOSAGE AND ADMINISTRATION.

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TABLE 4
Geometric Mean Concentrations (µg/mL) of Pneumococcal Antibodies Following Immunization of Children From 7 Months Through 9 Years of Age With Prevnar™²⁶

| Age group, Vaccinations | Study | Sample Size(s) | 4 | 6B | 9V | 14 | 18C | 19F | 23F |
|-------------------------|-------------|----------------|------|-------|------|-------|------|-------|-------|
| 7-11 mo. 3 doses | 118-12 | 22 | 2.34 | 3.66 | 2.11 | 9.33 | 2.31 | 1.60 | 2.50 |
| | 118-16 | 39 | 3.60 | 4.63 | 2.04 | 5.48 | 1.98 | 2.15 | 1.93 |
| 12-17 mo. 2 doses | 118-15* | 82-84† | 3.91 | 4.67 | 1.94 | 6.92 | 2.25 | 3.78 | 3.29 |
| | 118-18 | 33 | 7.02 | 4.25 | 3.26 | 6.31 | 3.60 | 3.29 | 2.92 |
| 18-23 mo. 2 doses | 118-15* | 52-54† | 3.36 | 4.92 | 1.80 | 6.69 | 2.65 | 3.17 | 2.71 |
| | 118-18 | 45 | 6.85 | 3.71 | 3.86 | 6.48 | 3.42 | 3.86 | 2.75 |
| 24-35 mo. 1 dose | 118-18 | 53 | 5.34 | 2.90 | 3.43 | 1.88 | 3.03 | 4.07 | 1.56 |
| 36-59 mo. 1 dose | 118-18 | 52 | 6.27 | 6.40 | 4.62 | 5.95 | 4.08 | 6.37 | 2.95 |
| 5-9 yrs. 1 dose | 118-18 | 101 | 6.92 | 20.84 | 7.49 | 19.32 | 6.72 | 12.51 | 11.57 |
| 118-8, DTaP | Post dose 3 | 31-32† | 1.47 | 2.18 | 1.52 | 5.05 | 2.24 | 1.54 | 1.48 |

195 Bold = GMC not inferior to 118-8, DTaP post dose 3 (one-sided lower limit of the 95% CI of GMC ratio ≥0.50).

* Study in Navajo and Apache populations.

† Numbers vary with serotype.

INDICATIONS AND USAGE

200 Prevnar™ is indicated for active immunization of infants and toddlers against invasive disease caused by *S. pneumoniae* due to capsular serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F). The routine schedule is 2, 4, 6, and 12-15 months of age. For additional information on usage, see DOSAGE AND ADMINISTRATION.

205 This vaccine is not intended to be used for treatment of active infection.

As with any vaccine, Prevnar™ may not protect 100% of individuals receiving the vaccine.

210 CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including diphtheria toxoid, is a contraindication to use of this vaccine.

215 The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. Although a severe or even a moderate febrile illness is sufficient reason to postpone vaccinations, minor illnesses, such as a mild upper respiratory infection with or without low-grade fever, are not generally contraindications.^{27,28}

220 WARNINGS

THIS VACCINE WILL NOT PROTECT AGAINST *S. PNEUMONIAE* DISEASE OTHER THAN THAT CAUSED BY THE SEVEN SEROTYPES INCLUDED IN THE VACCINE, NOR WILL IT PROTECT AGAINST OTHER MICROORGANISMS THAT CAUSE INVASIVE INFECTION SUCH AS BACTEREMIA AND
225 MENINGITIS.

This vaccine should not be given to infants or children with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration. If the decision is made to
230 administer this vaccine to children with coagulation disorders, it should be given with

caution. (See DRUG INTERACTIONS).

Immunization with Prevnar™ does not substitute for routine diphtheria immunization.

235 Healthcare professionals should prescribe and/or administer this product with caution to patients with a possible history of latex sensitivity since the packaging contains dry natural rubber.

PRECAUTIONS

240 Prevnar™ is for intramuscular use only. Prevnar™ SHOULD UNDER NO CIRCUMSTANCES BE ADMINISTERED INTRAVENOUSLY. The safety and immunogenicity for other routes of administration (e.g. subcutaneous) have not been evaluated.

245 General

CARE IS TO BE TAKEN BY THE HEALTHCARE PROFESSIONAL FOR THE SAFE AND EFFECTIVE USE OF THIS PRODUCT.

1. PRIOR TO ADMINISTRATION OF ANY DOSE OF THIS VACCINE, THE
250 PARENT OR GUARDIAN SHOULD BE ASKED ABOUT THE PERSONAL HISTORY, FAMILY HISTORY, AND RECENT HEALTH STATUS OF THE VACCINE RECIPIENT. THE HEALTHCARE PROFESSIONAL SHOULD ASCERTAIN PREVIOUS IMMUNIZATION HISTORY, CURRENT HEALTH STATUS, AND OCCURRENCE OF ANY SYMPTOMS AND/OR SIGNS OF AN
255 ADVERSE EVENT AFTER PREVIOUS IMMUNIZATIONS IN THE CHILD TO BE IMMUNIZED, IN ORDER TO DETERMINE THE EXISTENCE OF ANY CONTRAINDICATION TO IMMUNIZATION WITH THIS VACCINE AND TO ALLOW AN ASSESSMENT OF RISKS AND BENEFITS.

260 2. BEFORE THE ADMINISTRATION OF ANY BIOLOGICAL, THE HEALTHCARE PROFESSIONAL SHOULD TAKE ALL PRECAUTIONS

KNOWN FOR THE PREVENTION OF ALLERGIC OR ANY OTHER ADVERSE REACTIONS. This should include a review of the patient's history regarding possible sensitivity; the ready availability of epinephrine 1:1000 and other appropriate agents used for control of immediate allergic reactions; and a knowledge of the recent literature pertaining to use of the biological concerned, including the nature of side effects and adverse reactions that may follow its use.

3. Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents), a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunization.^{27,28,29} (See DRUG INTERACTIONS).

4. The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccine in children ≥ 24 months of age with sickle cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised. Data on sequential vaccination with PrevnarTM followed by 23-valent pneumococcal polysaccharide vaccine are limited. In a randomized study, 23 children ≥ 2 years of age with sickle cell disease were administered either 2 doses of PrevnarTM followed by a dose of polysaccharide vaccine or a single dose of polysaccharide vaccine alone. In this small study, safety and immune responses with the combined schedule were similar to polysaccharide vaccine alone.³⁰

5. Since this product is a suspension containing an aluminum adjuvant, shake vigorously immediately prior to use to obtain a uniform suspension prior to withdrawing the dose.
6. A separate sterile syringe and needle or a sterile disposable unit should be used for each individual to prevent transmission of hepatitis or other infectious agents from one person to another. Needles should be disposed of properly and should not be recapped.

7. Special care should be taken to prevent injection into or near a blood vessel or nerve.

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8. Healthcare professionals should prescribe and/or administer this product with caution to patients with a possible history of latex sensitivity since the packaging contains dry natural rubber.

300 **Information for Parents or Guardians**

Prior to administration of this vaccine, the healthcare professional should inform the parent, guardian, or other responsible adult of the potential benefits and risks to the patient (see ADVERSE REACTIONS and WARNINGS sections), and the importance of completing the immunization series unless contraindicated. Parents or guardians should
305 be instructed to report any suspected adverse reactions to their healthcare professional. The healthcare professional should provide vaccine information statements prior to each vaccination.

DRUG INTERACTIONS

310 Children receiving therapy with immunosuppressive agents (large amounts of corticosteroids, antimetabolites, alkylating agents, cytotoxic agents) may not respond optimally to active immunization.^{28,29,31,32} (See PRECAUTIONS, General).

As with other intramuscular injections, Prevnar™ should be given with caution to
315 children on anticoagulant therapy.

Simultaneous Administration with Other Vaccines

During clinical studies, Prevnar™ was administered simultaneously with DTP-HbOC or DTaP and HbOC, OPV or IPV, Hep B vaccines, MMR, and Varicella vaccine. Thus, the
320 safety experience with Prevnar™ reflects the use of this product as part of the routine immunization schedule.^{19,20,22,23,25}

The immune response to routine vaccines when administered with Prevnar™ (at separate sites) was assessed in 3 clinical studies in which there was a control group for

comparison. Results for the concurrent immunizations in infants are shown in Table 5 and for toddlers in Table 6. Enhancement of antibody response to HbOC in the infant series was observed. Some suppression of *Haemophilus influenzae* type b (Hib) response was seen at the 4th dose, but over 97% of children achieved titers ≥ 1 $\mu\text{g/mL}$. Although some inconsistent differences in response to pertussis antigens were observed, the clinical relevance is unknown. The response to 2 doses of IPV given concomitantly with PlevnarTM, assessed 3 months after the second dose, was equivalent to controls for poliovirus Types 2 and 3, but lower for Type 1. MMR and Varicella immunogenicity data from controlled clinical trials with concurrent administration of PlevnarTM are not available.

TABLE 5
Concurrent Administration of PlevnarTM With Other Vaccines to Infants in
Non-Efficacy Studies^{20,23}

| Antigen* | GMC* | | % Responders [†] | | Study | Vaccine Schedule [‡] (mo.) | N | |
|------------|-----------------------|----------------------|---------------------------|----------------------|--------|--|-----------------------|----------------------|
| | Plevnar TM | Control [§] | Plevnar TM | Control [§] | | | Plevnar TM | Control [§] |
| Hib | 6.2 | 4.4 | 99.5, 88.3 | 97.0, 88.1 | 118-12 | 2, 4, 6 | 214 | 67 |
| Diphtheria | 0.9 | 0.8 | 100 | 97.0 | | | | |
| Tetanus | 3.5 | 4.1 | 100 | 100 | | | | |
| PT | 19.1 | 17.8 | 74.0 | 69.7 | | | | |
| FHA | 43.8 | 46.7 | 66.4 | 69.7 | | | | |
| Pertactin | 40.1 | 50.9 | 65.6 | 77.3 | | | | |
| Fimbriae 2 | 3.3 | 4.2 | 44.7 | 62.5 | | | | |
| Hib | 11.9 | 7.8 | 100, 96.9 | 98.8, 92.8 | 118-16 | 2, 4, 6 | 159 | 83 |
| Hep B | -- | -- | 99.4 | 96.2 | 118-16 | 0, 2, 6 | 156 | 80 |
| IPV Type 1 | -- | -- | 89.0 | 93.6 | 118-16 | 2, 4 | 156 | 80 |
| Type 2 | -- | -- | 94.2 | 93.6 | | | | |
| Type 3 | -- | -- | 83.8 | 80.8 | | | | |

* Hib vaccine was HibTITER®, DTaP vaccine was Acel-Imune®. Hib ($\mu\text{g/mL}$); Dip, Tet (IU/mL); Pertussis Antigens (PT, FHA, Ptn, Fim) (units/mL).

[†] Responders = Hib (≥ 0.15 $\mu\text{g/mL}$, ≥ 1.0 $\mu\text{g/mL}$); Dip, Tet (≥ 0.1 IU/mL); Pertussis Antigens (PT, FHA, Ptn, Fim) [4-fold rise]; IPV ($\geq 1:10$); Hep B (≥ 10 mIU/mL).

[‡] Schedule for concurrently administered vaccines; PlevnarTM administered at 2, 4, 6 mos.; blood for antibody assessment attained 1 month after third dose, except for IPV (3 months post-immunization).

[§] Concurrent vaccines only.

^{||} $p < 0.05$ when PlevnarTM compared to control group using the following tests: ANCOVA for GMCs in 118-12; ANOVA for GMCs in 118-16; and Fisher's Exact test for % Responders in 118-12.

[†] Lower bound of 90% CI of difference $> 10\%$.

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TABLE 6
Concurrent Administration of Prevnar™ With Other Vaccines to Toddlers in a
Non-Efficacy Study²²

| Antigen [†] | GMC [*] | | % Responders [†] | | Study [†] | Vaccine Schedule [‡] (mo.) | N | |
|----------------------|------------------|----------------------|---------------------------|----------------------|--------------------|--|----------|----------------------|
| | Prevnar™ | Control [¶] | Prevnar™ | Control [¶] | | | Prevnar™ | Control [¶] |
| Hib | 22.7 | 47.9 [¶] | 100, 97.9 | 100, 100 | 118-7 | 12-15 | 47 | 26 |
| Diphtheria | 2.0 | 3.2 [¶] | 100 | 100 | | | | |
| Tetanus | 14.4 | 18.8 | 100 | 100 | | | | |
| PT | 68.6 | 121.2 [¶] | 68.1 | 73.1 | | | | |
| FHA | 29.0 | 48.2 [¶] | 68.1 | 84.6 | | | | |
| Pertactin | 84.4 | 83.0 | 83.0 | 96.2 | | | | |
| Fimbriae 2 | 5.2 | 3.8 | 63.8 | 50.0 | | | | |

^{*} Hib vaccine was HibTITER®, DTaP vaccine was Acel-Imune®. Hib (µg/mL); Dip, Tet (IU/mL); Pertussis Antigens (PT, FHA, Ptn, Fim) (units/mL).

[†] Responders = Hib (≥0.15 µg/mL, ≥1.0 µg/mL); Dip, Tet (≥0.1 IU/mL); Pertussis Antigens (PT, FHA, Ptn, Fim) [4-fold rise].

[‡] Children received a primary series of DTP-HbOC (Tetramune®).

[§] Blood for antibody assessment obtained 1 month after dose.

[¶] Concurrent vaccines only.

^{††} p<0.05 when Prevnar™ compared to control group using a two-sample t-test.

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CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Prevnar™ has not been evaluated for any carcinogenic or mutagenic potential, or impairment of fertility.

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PREGNANCY

Pregnancy Category C

Animal reproductive studies have not been conducted with this product. It is not known whether Prevnar™ can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. This vaccine is not recommended for use in pregnant women.

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Nursing Mothers

It is not known whether vaccine antigens or antibodies are excreted in human milk. This vaccine is not recommended for use in a nursing mother.

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380 **PEDIATRIC USE**

Prevnar™ has been shown to be usually well-tolerated and immunogenic in infants. The safety and effectiveness of Prevnar™ in children below the age of 6 weeks have not been established. Immune responses elicited by Prevnar™ among infants born prematurely have not been studied. See DOSAGE AND ADMINISTRATION for the recommended
385 pediatric dosage.

GERIATRIC USE

This vaccine is NOT recommended for use in adult populations. It is not to be used as a substitute for the pneumococcal polysaccharide vaccine, in geriatric populations.

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ADVERSE REACTIONS

The majority of the safety experience with Prevnar™ comes from the NCKP Efficacy Trial in which 17,066 infants received 55,352 doses of Prevnar™, along with other routine childhood vaccines through April 1998 (see CLINICAL PHARMACOLOGY
395 section). The number of Prevnar™ recipients in the safety analysis differs from the number included in the efficacy analysis due to the different lengths of follow-up for these study endpoints. Safety was monitored in this study using several modalities. Local reactions and systemic events occurring within 48 hours of each dose of vaccine were ascertained by scripted telephone interview on a randomly selected subset of
400 approximately 3,000 children in each vaccine group. The rate of relatively rare events requiring medical attention was evaluated across all doses in all study participants using automated databases. Specifically, rates of hospitalizations within 3, 14, 30, and 60 days of immunization, and of emergency room visits within 3, 14, and 30 days of immunization were assessed and compared between vaccine groups for each diagnosis.
405 Seizures within 3 and 30 days of immunization were ascertained across multiple settings (hospitalizations, emergency room or clinic visits, telephone interviews). Deaths and SIDS were ascertained through April 1999. Hospitalizations due to diabetes, autoimmune disorders, and blood disorders were ascertained through August 1999.

410

In Tables 7 and 8, the rate of local reactions at the Prevnar™ injection site is compared at each dose to the DTP or DTap injection site in the same children.

TABLE 7
Percentage of Subjects Reporting Local Reactions Within 2 Days Following Immunization With Prevnar™ and DTP-HbOC* Vaccines at 2, 4, 6, and 12-15 Months of Age[†]

| <u>Reaction</u> | <u>Dose 1</u> | | <u>Dose 2</u> | | <u>Dose 3</u> | | <u>Dose 4</u> | |
|-------------------------------|--------------------------|--------------------------------|--------------------------|--------------------------------|--------------------------|--------------------------------|--------------------------|--------------------------------|
| | <u>Prevnar™ Site</u> | <u>DTP- HbOC Site†</u> | <u>Prevnar™ Site</u> | <u>DTP- HbOC Site†</u> | <u>Prevnar™ Site</u> | <u>DTP- HbOC Site†</u> | <u>Prevnar™ Site</u> | <u>DTP- HbOC Site†</u> |
| | N=2890 | N=2890 | N=2725 | N=2725 | N=2538 | N=2538 | N=599 | N=599 |
| Erythema | | | | | | | | |
| Any | 12.4 | 21.9 | 14.3 | 25.1 | 15.2 | 26.5 | 12.7 | 23.4 |
| > 2.4 cm | 1.2 | 4.6 | 1.0 | 2.9 | 2.0 | 4.4 | 1.7 | 6.4 |
| Induration | | | | | | | | |
| Any | 10.9 | 22.4 | 12.3 | 23.0 | 12.8 | 23.3 | 11.4 | 20.5 |
| > 2.4 cm | 2.6 | 7.2 | 2.4 | 5.6 | 2.9 | 6.7 | 2.8 | 7.2 |
| Tenderness | | | | | | | | |
| Any | 28.0 | 36.4 | 25.2 | 30.5 | 25.6 | 32.8 | 36.5 | 45.1 |
| Interfered with limb movement | 7.9 | 10.7 | 7.4 | 8.4 | 7.8 | 10.0 | 18.5 | 22.2 |

* If Hep B vaccine was administered simultaneously, it was administered into the same limb as the DTP-HbOC vaccine. If reactions occurred at either or both sites on that limb, the more severe reaction was recorded.

† p<0.05 when Prevnar™ site compared to the DTP-HbOC site using the sign test.

TABLE 8
Percentage of Subjects Reporting Local Reactions Within 2 Days Following Immunization
with Prevnar™* and DTaP Vaccines† at 2, 4, 6, and 12-15 Months of Age¹⁹

| <u>Reaction</u> | <u>Dose 1</u> | | <u>Dose 2</u> | | <u>Dose 3</u> | | <u>Dose 4</u> | |
|-------------------------------|--------------------------------|----------------------------|--------------------------------|----------------------------|--------------------------------|----------------------------|--------------------------------|-----------------------------|
| | <u>Prevnar™</u> <u>Site</u> | <u>DTaP</u> <u>Site</u> | <u>Prevnar™</u> <u>Site</u> | <u>DTaP</u> <u>Site</u> | <u>Prevnar™</u> <u>Site</u> | <u>DTaP</u> <u>Site</u> | <u>Prevnar™</u> <u>Site</u> | <u>DTaP</u> <u>Site†</u> |
| | N=693 | N=693 | N=526 | N=526 | N=422 | N=422 | N=165 | N=165 |
| Erythema | | | | | | | | |
| Any | 10.0 | 6.7§ | 11.6 | 10.5 | 13.8 | 11.4 | 10.9 | 3.6§ |
| > 2.4 cm | 1.3 | 0.4§ | 0.6 | 0.6 | 1.4 | 1.0 | 3.6 | 0.6 |
| Induration | | | | | | | | |
| Any | 9.8 | 6.6§ | 12.0 | 10.5 | 10.4 | 10.4 | 12.1 | 5.5§ |
| > 2.4 cm | 1.6 | 0.9 | 1.3 | 1.7 | 2.4 | 1.9 | 5.5 | 1.8 |
| Tenderness | | | | | | | | |
| Any | 17.9 | 16.0 | 19.4 | 17.3 | 14.7 | 13.1 | 23.3 | 18.4 |
| Interfered with limb movement | 3.1 | 1.8§ | 4.1 | 3.3 | 2.9 | 1.9 | 9.2 | 8.0 |

420 * HbOC was administered in the same limb as Prevnar™. If reactions occurred at either or both sites on that limb, the more severe reaction was recorded.

† If Hep B vaccine was administered simultaneously, it was administered into the same limb as DTaP. If reactions occurred at either or both sites on that limb, the more severe reaction was recorded.

425 ‡ Subjects may have received DTP or a mixed DTP/DTaP regimen for the primary series. Thus, this is the 4th dose of a pertussis vaccine, but not a 4th dose of DTaP.

§ p<0.05 when Prevnar™ site compared to DTaP site using the sign test.

430 Table 9 presents the rates of local reactions in previously unvaccinated older infants and children.

TABLE 9
Percentage of Subjects Reporting Local Reactions Within 3 Days of Immunization
in Infants and Children from 7 Months Through 9 Years of Age²⁴

| Age at 1st Vaccination | 7 - 11 Mos. | | | | | | 12 - 23 Mos. | | | 24 - 35 Mos. | 36 - 59 Mos. | 5 - 9 Yrs. |
|--|-------------|------|----------------|--------|------|----------------|--------------|--------|------|--------------|--------------|------------|
| Study No. | 118-12 | | | 118-16 | | | 118-9* | 118-18 | | 118-18 | 118-18 | 118-18 |
| Dose Number | 1 | 2 | 3 [†] | 1 | 2 | 3 [†] | 1 | 1 | 2 | 1 | 1 | 1 |
| Number of Subjects | 54 | 51 | 24 | 81 | 76 | 50 | 60 | 114 | 117 | 46 | 48 | 49 |
| Reaction | | | | | | | | | | | | |
| Erythema | | | | | | | | | | | | |
| Any | 16.7 | 11.8 | 20.8 | 7.4 | 7.9 | 14.0 | 48.3 | 10.5 | 9.4 | 6.5 | 29.2 | 24.2 |
| > 2.4 cm [‡] | 1.9 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 6.7 | 1.8 | 1.7 | 0.0 | 8.3 | 7.1 |
| Induration | | | | | | | | | | | | |
| Any | 16.7 | 11.8 | 8.3 | 7.4 | 3.9 | 10.0 | 48.3 | 8.8 | 6.0 | 10.9 | 22.9 | 25.5 |
| > 2.4 cm [‡] | 3.7 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 3.3 | 0.9 | 0.9 | 2.2 | 6.3 | 9.3 |
| Tenderness | | | | | | | | | | | | |
| Any | 13.0 | 11.8 | 12.5 | 8.6 | 10.5 | 12.0 | 46.7 | 25.7 | 26.5 | 41.3 | 58.3 | 82.8 |
| Interfered with limb movement [§] | 1.9 | 2.0 | 4.2 | 1.2 | 1.3 | 0.0 | 3.3 | 6.2 | 8.5 | 13.0 | 20.8 | 39.4 |

435 * For 118-9, 2 of 60 subjects were ≥24 months of age.

† For 118-12, dose 3 was administered at 15 - 18 mos. of age. For 118-16, dose 3 was administered at 12 - 15 mos. of age.

‡ For 118-16 and 118-18, ≥2 cm.

§ Tenderness interfering with limb movement.

440

Tables 10 and 11 present the rates of systemic events observed in the efficacy study when Prevnar™ was administered concomitantly with DTP or DTaP.

TABLE 10
Percentage of Subjects* Reporting Systemic Events Within 2 Days Following Immunization with Prevnar™ or Control† Vaccine Concurrently With DTP-HbOC Vaccine at 2, 4, 6, and 12-15 Months of Age[‡]

| Reaction | Dose 1 | | Dose 2 | | Dose 3 | | Dose 4 | |
|--------------------|----------|----------|----------|----------|----------|----------|----------|----------|
| | Prevnar™ | Control† | Prevnar™ | Control† | Prevnar™ | Control† | Prevnar™ | Control† |
| | N=2998 | N=2982 | N=2788 | N=2761 | N=2596 | N=2591 | N=709 | N=733 |
| Fever | | | | | | | | |
| ≥ 38.0°C | 33.4 | 28.7‡ | 34.7 | 27.4‡ | 40.6 | 32.4‡ | 41.9 | 36.9 |
| > 39.0°C | 1.3 | 1.3 | 3.0 | 1.6‡ | 5.3 | 3.4‡ | 4.5 | 4.5 |
| Irritability | 71.3 | 67.9‡ | 69.4 | 63.8‡ | 68.9 | 61.6‡ | 72.8 | 65.8‡ |
| Drowsiness | 49.2 | 50.6 | 32.5 | 33.6 | 25.9 | 23.4‡ | 21.3 | 22.7 |
| Restless Sleep | 18.1 | 17.9 | 27.3 | 24.3‡ | 33.3 | 30.1‡ | 29.9 | 28.0 |
| Decreased Appetite | 24.7 | 23.6 | 22.8 | 20.3‡ | 27.7 | 25.6 | 33.0 | 27.4‡ |
| Vomiting | 17.9 | 14.9‡ | 16.2 | 14.4 | 15.5 | 12.7‡ | 9.6 | 6.8 |
| Diarrhea | 12.0 | 10.7 | 10.9 | 9.9 | 11.5 | 10.4 | 12.1 | 11.2 |
| Rash or Hives | 0.7 | 0.6 | 0.8 | 0.8 | 1.4 | 1.1 | 1.4 | 0.8 |

445 * Approximately 90% of subjects received prophylactic or therapeutic antipyretics within 48 hours of each dose.

† Investigational meningococcal group C conjugate vaccine (MnCC).

‡ p<0.05 when Prevnar™ compared to control group using a Chi-Square test.

450

TABLE 11
Percentage of Subjects* Reporting Systemic Events Within 2 Days Following Immunization With Prevnar™ or Control† Vaccine Concurrently With DTaP Vaccine at 2, 4, 6, and 12-15 Months of Age[‡]

| Reaction | Dose 1 | | Dose 2 | | Dose 3 | | Dose 4‡ | |
|--------------------|----------|----------|----------|----------|----------|----------|----------|----------|
| | Prevnar™ | Control† | Prevnar™ | Control† | Prevnar™ | Control† | Prevnar™ | Control† |
| | N=710 | N=711 | N=559 | N=508 | N=461 | N=414 | N=224 | N=230 |
| Fever | | | | | | | | |
| ≥ 38.0°C | 15.1 | 9.4§ | 23.9 | 10.8§ | 19.1 | 11.8§ | 21.0 | 17.0 |
| > 39.0°C | 0.9 | 0.3 | 2.5 | 0.8§ | 1.7 | 0.7 | 1.3 | 1.7 |
| Irritability | 48.0 | 48.2 | 58.7 | 45.3§ | 51.2 | 44.8 | 44.2 | 42.6 |
| Drowsiness | 40.7 | 42.0 | 25.6 | 22.8 | 19.5 | 21.9 | 17.0 | 16.5 |
| Restless Sleep | 15.3 | 15.1 | 20.2 | 19.3 | 25.2 | 19.0§ | 20.2 | 19.1 |
| Decreased Appetite | 17.0 | 13.5 | 17.4 | 13.4 | 20.7 | 13.8§ | 20.5 | 23.1 |
| Vomiting | 14.6 | 14.5 | 16.8 | 14.4 | 10.4 | 11.6 | 4.9 | 4.8 |
| Diarrhea | 11.9 | 8.4§ | 10.2 | 9.3 | 8.3 | 9.4 | 11.6 | 9.2 |
| Rash or Hives | 1.4 | 0.3§ | 1.3 | 1.4 | 0.4 | 0.5 | 0.5 | 1.7 |

* Approximately 75% of subjects received prophylactic or therapeutic antipyretics within 48 hours of each dose.

† Investigational meningococcal group C conjugate vaccine (MnCC).

‡ Most of these children had received DTP for the primary series. Thus, this is a 4th dose of a pertussis vaccine, but not of DTaP.

§ p<0.05 when Prevnar™ compared to control group using a Chi-Square test.

455

460 Table 12 presents results from a second study (Manufacturing Bridging Study) conducted
at Northern California and Denver Kaiser sites, in which children were randomized to
receive one of three lots of Prevnar™ with concomitant vaccines including DTaP, or the
same concomitant vaccines alone. Information was ascertained by scripted telephone
interview, as described above.

465

TABLE 12
Percentage of Subjects* Reporting Systemic Reactions Within 3 Days Following
Immunization With Prevnar™, DTaP, HbOC, Hep B, and IPV vs. Control†
In Manufacturing Bridging Study²⁰

| <u>Reaction</u> | <u>Dose 1</u> | | <u>Dose 2</u> | | <u>Dose 3</u> | |
|--------------------|---------------|----------|---------------|----------|---------------|----------|
| | Prevnar™ | Control† | Prevnar™ | Control† | Prevnar™ | Control† |
| | N=498 | N=108 | N=452 | N=99 | N=445 | N=89 |
| Fever | | | | | | |
| ≥ 38.0°C | 21.9 | 10.2‡ | 33.6 | 17.2‡ | 28.1 | 23.6 |
| > 39.0°C | 0.8 | 0.9 | 3.8 | 0.0 | 2.2 | 0.0 |
| Irritability | 59.7 | 60.2 | 65.3 | 52.5‡ | 54.2 | 50.6 |
| Drowsiness | 50.8 | 38.9‡ | 30.3 | 31.3 | 21.2 | 20.2 |
| Decreased Appetite | 19.1 | 15.7 | 20.6 | 11.1‡ | 20.4 | 9.0‡ |

* Approximately 72% of subjects received prophylactic or therapeutic antipyretics within 48 hours of each dose.

† Control group received concomitant vaccines only in the same schedule as the Prevnar™ group (DTaP, HbOC at dose 1, 2, 3; IPV at doses 1 and 2; Hep B at doses 1 and 3).

‡ p<0.05 when Prevnar™ compared to control group using Fisher's Exact test.

470

Fever (≥ 38.0°C) within 48 hours of a vaccine dose was reported by a greater proportion
of subjects who received Prevnar™, compared to control (investigational meningococcal
group C conjugate vaccine [MnCC]), after each dose when administered concurrently
with DTP-HbOC or DTaP in the efficacy study. In the Manufacturing Bridging Study,
fever within 48-72 hours was also reported more commonly after each dose compared to
infants in the control group who received only recommended vaccines. When
administered concurrently with DTaP in either study, fever rates among Prevnar™
recipients ranged from 15% to 34%, and were greatest after the 2nd dose.

480

Table 13 presents the frequencies of systemic reactions in previously unvaccinated older infants and children.

485

TABLE 13
Percentage of Subjects Reporting Systemic Reactions Within 3 Days of Immunization
in Infants and Children from 7 Months Through 9 Years of Age²⁶

| Age at 1st Vaccination | 7 - 11 Mos. | | | | | | 12 - 23 Mos. | | | 24 - 35 Mos. | 36 - 59 Mos. | 5 - 9 Yrs. |
|------------------------|-------------|------|------|--------|------|------|--------------|--------|------|--------------|--------------|------------|
| Study No. | 118-12 | | | 118-16 | | | 118-9* | 118-18 | | 118-18 | 118-18 | 118-18 |
| Dose Number | 1 | 2 | 3† | 1 | 2 | 3† | 1 | 1 | 2 | 1 | 1 | 1 |
| Number of Subjects | 54 | 51 | 24 | 85 | 80 | 50 | 60 | 120 | 117 | 47 | 52 | 100 |
| Reaction | | | | | | | | | | | | |
| Fever ≥ 38.0°C | 20.8 | 21.6 | 25.0 | 17.6 | 18.8 | 22.0 | 36.7 | 11.7 | 6.8 | 14.9 | 11.5 | 7.0 |
| > 39.0°C | 1.9 | 5.9 | 0.0 | 1.6 | 3.9 | 2.6 | 0.0 | 4.4 | 0.0 | 4.2 | 2.3 | 1.2 |
| Fussiness | 29.6 | 39.2 | 16.7 | 54.1 | 41.3 | 38.0 | 40.0 | 37.5 | 36.8 | 46.8 | 34.6 | 29.3 |
| Drowsiness | 11.1 | 17.6 | 16.7 | 24.7 | 16.3 | 14.0 | 13.3 | 18.3 | 11.1 | 12.8 | 17.3 | 11.0 |
| Decreased Appetite | 9.3 | 15.7 | 0.0 | 15.3 | 15.0 | 30.0 | 25.0 | 20.8 | 16.2 | 23.4 | 11.5 | 9.0 |

* For 118-9, 2 of 60 subjects were ≥24 months of age.

490 † For 118-12, dose 3 was administered at 15 - 18 mos. of age. For 118-16, dose 3 was administered at 12 - 15 mos. of age.

Of the 17,066 subjects who received at least one dose of Plevnar™ in the efficacy trial,
 495 there were 24 hospitalizations (for 29 diagnoses) within 3 days of a dose from October 1995 through April 1998. Diagnoses were as follows: bronchiolitis (5); congenital anomaly (4); elective procedure, UTI (3 each); acute gastroenteritis, asthma, pneumonia (2 each); aspiration, breath holding, influenza, inguinal hernia repair, otitis media, febrile seizure, viral syndrome, well child/reassurance (1 each). There were 162 visits to the
 500 emergency room (for 182 diagnoses) within 3 days of a dose from October 1995 through April 1998. Diagnoses were as follows: febrile illness (20); acute gastroenteritis (19); trauma, URI (16 each); otitis media (15); well child (13); irritable child, viral syndrome (10 each); rash (8); croup, pneumonia (6 each); poisoning/ingestion (5); asthma, bronchiolitis (4 each); febrile seizure, UTI (3 each); thrush, wheezing, breath holding,
 505 choking, conjunctivitis, inguinal hernia repair, pharyngitis (2 each); colic, colitis,

congestive heart failure, elective procedure, hives, influenza, ingrown toenail, local swelling, roseola, sepsis (1 each).¹⁹

One case of a hypotonic-hyporesponsive episode (HHE) was reported in the efficacy study following PrevnarTM and concurrent DTP vaccines in the study period from October 1995 through April 1998. Two additional cases of HHE were reported in four other studies and these also occurred in children who received PrevnarTM concurrently with DTP vaccine.^{22,25}

In the Kaiser efficacy study in which 17,066 children received a total of 55,352 doses of PrevnarTM and 17,080 children received a total of 55,387 doses of the control vaccine (investigational meningococcal group C conjugate vaccine [MnCC]), seizures were reported in 8 PrevnarTM recipients and 4 control vaccine recipients within 3 days of immunization from October 1995 through April 1998. Of the 8 PrevnarTM recipients, 7 received concomitant DTP-containing vaccines and one received DTaP. Of the 4 control vaccine recipients, 3 received concomitant DTP-containing vaccines and one received DTaP.¹⁹ In the other 4 studies combined, in which 1,102 children were immunized with 3,347 doses of PrevnarTM and 408 children were immunized with 1,310 doses of control vaccine (either investigational meningococcal group C conjugate vaccine [MnCC] or concurrent vaccines), there was one seizure event reported within 3 days of immunization.²³ This subject received PrevnarTM concurrent with DTaP vaccine.

Twelve deaths (5 SIDS and 7 with clear alternative cause) occurred among subjects receiving PrevnarTM, of which 11 (4 SIDS and 7 with clear alternative cause) occurred in the Kaiser efficacy study from October 1995 until April 20, 1999. In comparison, 21 deaths (8 SIDS, 12 with clear alternative cause and one SIDS-like death in an older child), occurred in the control vaccine group during the same time period in the efficacy study.^{19,20} The number of SIDS deaths in the efficacy study from October 1995 until April 20, 1999 were similar to or lower than the age and season-adjusted expected rate from the California State data from 1995-1997 and are presented in Table 14.

TABLE 14
Age and Season-Adjusted Comparison of SIDS Rates in the NCKP Efficacy Trial
With the Expected Rate from the California State Data for 1995-1997¹⁹

| Vaccine | < One Week | | ≤ Two Weeks | | ≤ One Month | | ≤ One Year | |
|-----------------------|--------------------|-----|--------------------|-----|--------------------|-----|--------------------|-----|
| | After Immunization | | After Immunization | | After Immunization | | After Immunization | |
| | Exp | Obs | Exp | Obs | Exp | Obs | Exp | Obs |
| Prevnam TM | 1.06 | 1 | 2.09 | 2 | 4.28 | 2 | 8.08 | 4 |
| Control* | 1.06 | 2 | 2.09 | 3† | 4.28 | 3† | 8.08 | 8† |

* Investigational meningococcal group C conjugate vaccine (MnCC).

540 † Does not include one additional case of SIDS-like death in a child older than the usual SIDS age (448 days).

In a review of all hospitalizations that occurred between October 1995 and August 1999 in the efficacy study for the specific diagnoses of aplastic anemia, autoimmune disease,
545 autoimmune hemolytic anemia, diabetes mellitus, neutropenia, and thrombocytopenia, the numbers of such cases were equal to or less than the expected numbers based on the 1995 Kaiser Vaccine Safety Data Link (VSD) data set.

Overall, the safety of PrevnamTM has been evaluated in a total of five clinical studies in
550 which 18,168 infants and children received a total of 58,699 doses of vaccine at 2, 4, 6, and 12-15 months of age. In addition, the safety of PrevnamTM was evaluated in 560 children from 4 ancillary studies who started immunization at 7 months to 9 years of age. Tables 15 and 16 summarize systemic reactogenicity data within 2 or 3 days across 4,748 subjects (13,039 infant doses and 1,706 toddler doses) for whom these data were
555 collected and according to the pertussis vaccine administered concurrently.

TABLE 15

**Overall Percentage of Doses Associated With Systemic Events Within 2 or 3 Days
For Efficacy Study and All Ancillary Studies When Prevnar™ Administered To
Infants As a Primary Series at 2, 4, and 6 Months of Age^{19,20,22,23,25}**

| Systemic Event | Prevnar™ Concurrently With DTP-HbOC (9,191 Doses)* | Prevnar™ Concurrently With DTaP and HbOC (3,848 Doses)† | DTaP and HbOC Control (538 Doses)‡ |
|---------------------------|---|--|---|
| Fever | | | |
| ≥ 38.0°C | 35.6 | 21.1 | 14.2 |
| > 39.0°C | 3.1 | 1.8 | 0.4 |
| Irritability | 69.1 | 52.5 | 45.2 |
| Drowsiness | 36.9 | 32.9 | 27.7 |
| Restless Sleep | 25.8 | 20.6 | 22.3 |
| Decreased Appetite | 24.7 | 18.1 | 13.6 |
| Vomiting | 16.2 | 13.4 | 9.8 |
| Diarrhea | 11.4 | 9.8 | 4.4 |
| Rash or Hives | 0.9 | 0.6 | 0.3 |

* Total from which reaction data are available varies between reactions from 8,874-9,191 doses.
Data from studies 118-3, 118-7, 118-8.

† Total from which reaction data are available varies between reactions from 3,121-3,848 doses.
Data from studies 118-8, 118-12, 118-16.

‡ Total from which reaction data are available varies between reactions from 295-538 doses.
Data from studies 118-12 and 118-16.

TABLE 16

Overall Percentage of Doses Associated With Systemic Events Within 2 or 3 Days
For Efficacy Study and All Ancillary Studies When Prevnar™ Administered To
Toddlers as a Fourth Dose At 12 to 15 Months of Age^{19,22}

| Systemic Event | Prevnam™ Concurrently With DTP-HbOC (709 Doses)* | Prevnam™ Concurrently With DTaP and HbOC (270 Doses)† | Prevnam™ Only No Concurrent Vaccines (727 Doses)‡ |
|---------------------------|---|--|---|
| Fever | | | |
| ≥ 38.0°C | 41.9 | 19.6 | 13.4 |
| > 39.0°C | 4.5 | 1.5 | 1.2 |
| Irritability | 72.8 | 45.9 | 45.8 |
| Drowsiness | 21.3 | 17.5 | 15.9 |
| Restless Sleep | 29.9 | 21.2 | 21.2 |
| Decreased Appetite | 33.0 | 21.1 | 18.3 |
| Vomiting | 9.6 | 5.6 | 6.3 |
| Diarrhea | 12.1 | 13.7 | 12.8 |
| Rash or Hives | 1.4 | 0.7 | 1.2 |

* Total from which reaction data are available varies between reactions from 706-709 doses.
Data from study 118-8.

† Total from which reaction data are available varies between reactions from 269-270 doses.
Data from studies 118-7 and 118-8.

‡ Total from which reaction data are available varies between reactions from 725-727 doses.
Data from studies 118-7 and 118-8.

With vaccines in general, including Prevnar™, it is not uncommon for patients to note within 48 to 72 hours at or around the injection site the following minor reactions: edema; pain or tenderness; redness, inflammation or skin discoloration; mass; or local hypersensitivity reaction. Such local reactions are usually self-limited and require no therapy.

As with other aluminum-containing vaccines, a nodule may occasionally be palpable at the injection site for several weeks.³³

ADVERSE EVENT REPORTING

590 Any suspected adverse events following immunization should be reported by the
healthcare professional to the US Department of Health and Human Services (DHHS).
The National Vaccine Injury Compensation Program requires that the manufacturer and
lot number of the vaccine administered be recorded by the healthcare professional in the
vaccine recipient's permanent medical record (or in a permanent office log or file), along
595 with the date of administration of the vaccine and the name, address, and title of the
person administering the vaccine.

The US DHHS has established the Vaccine Adverse Event Reporting System (VAERS)
to accept all reports of suspected adverse events after the administration of any vaccine
600 including, but not limited to, the reporting of events required by the National Childhood
Vaccine Injury Act of 1986. The FDA web site is:

<http://www.fda.gov/cber/vaers/vaers.htm>.

The VAERS toll-free number for VAERS forms and information is 800-822-7967.³⁴

DOSAGE AND ADMINISTRATION

For intramuscular injection only. *Do not inject intravenously.*

The dose is 0.5 mL to be given intramuscularly.

Since this product is a suspension containing an adjuvant, shake vigorously
610 immediately prior to use to obtain a uniform suspension in the vaccine container.
The vaccine should not be used if it cannot be resuspended.

After shaking, the vaccine is a homogeneous, white suspension.

615 Parenteral drug products should be inspected visually for particulate matter and
discoloration prior to administration (see DESCRIPTION). This product should not be
used if particulate matter or discoloration is found.

The vaccine should be injected intramuscularly. The preferred sites are the anterolateral

620 aspect of the thigh in infants or the deltoid muscle of the upper arm in toddlers and young
children. The vaccine should not be injected in the gluteal area or areas where there may
be a major nerve trunk and/or blood vessel. Before injection, the skin at the injection site
should be cleansed and prepared with a suitable germicide. After insertion of the needle,
aspirate and wait to see if any blood appears in the syringe, which will help avoid
625 inadvertent injection into a blood vessel. If blood appears, withdraw the needle and
prepare for a new injection at another site.

Vaccine Schedule

For infants, the immunization series of Prevnar™ consists of three doses of 0.5 mL each,
630 at approximately 2-month intervals, followed by a fourth dose of 0.5 mL at 12-15 months
of age. The customary age for the first dose is 2 months of age, but it can be given as
young as 6 weeks of age. The recommended dosing interval is 4 to 8 weeks. The fourth
dose should be administered at least 2 months after the third dose.

635 Previously Unvaccinated Older Infants and Children

For previously unvaccinated older infants and children, who are beyond the age of the
routine infant schedule, the following schedule applies:²⁶

| Age at First Dose | Total Number of 0.5 mL Doses |
|------------------------------------|------------------------------|
| 7-11 months of age | 3* |
| 12-23 months of age | 2† |
| ≥ 24 months through 9 years of age | 1 |

640 * 2 doses at least 4 weeks apart; third dose after the one-year birthday,
separated from the second dose by at least 2 months.

† 2 doses at least 2 months apart.

(See CLINICAL PHARMACOLOGY section for the limited available immunogenicity
data and ADVERSE EVENTS section for limited safety data corresponding to the
645 previously noted vaccination schedule for older children).

Safety and immunogenicity data are either limited or not available for children in specific

high risk groups for invasive pneumococcal disease (e.g. persons with sickle cell disease, asplenia, HIV-infected).

650

HOW SUPPLIED

Vial, 1 Dose (5 per package) - NDC 0005-1970-67

CPT Code 90669

655

STORAGE

DO NOT FREEZE. STORE REFRIGERATED, AWAY FROM FREEZER COMPARTMENT, AT 2°C TO 8°C (36°F TO 46°F).

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